Office Action, the Examiner stated that amendments to the claims in accordance with the proposed claim set would be entered and would put the application into condition for allowance. Applicants have amended the claims in accordance with the claims set forth by the Examiner. Claims 1, 2, 8, 9, 11, 17, 39, 40, 44, 45, 47-49 and 51 are identical to those faxed by the Examiner, except that Applicants incorporated the fusion step into step a), instead of making it a separate step b). Support for fusion of the oocyte and donor cell can be found throughout the specification and, in particular, on page 9, lines 16-22; on page 11, line 23 through page 12, line 7; and on page 30, line 7 through page 33, line 5. Claims 2, 9, 17, 40 and new Claims 61, 64, 68, 72, 76, and 80 now have the limitation that the activated donor cell is in the G_1 stage of mitotic cell cycle, and excluding S phase, and G_2/M phase, as suggested by the Examiner. The balance of the amendments have been made to fix typographical errors and/or antecedent basis.

New Claims 60-83 have been added and depend on one of the following pending, independent claims: Claims 44, 45, 47, 48, 49, or 51. These claims mirror pending Claims 2, 4, 5, and 7 but depend on the independent claims recited.

Lastly, new Claims 84-93 mirror the amended independent claims, and contain language that is similar to that in original Claim 20, which the Examiner has indicated to be allowable in her facsimile of November 15, 2001. Instead of stating that the activated donor cell and the enucleated, activated oocyte are fused, these new claims state that the nucleus of the donor cell is injected into the oocyte. Support for injecting a donor cell nucleus into the oocyte can be found in the specification, on page 3, lines 8-11; page 11, lines 14-22; and Example 1, page 23, lines 17-20. No new matter is added.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) was filed on April 9, 2002. Entry of the SIDS is respectfully requested.

Additionally, Applicants filed a SIDS with a two page Form 1449 on August 21, 2000. Accompanying the Office Action dated March 28, 2001, Applicants received only page two of the Form 1449, signed and initialed by the Examiner. Page one was missing. Applicants respectfully request that the Examiner attach the first page, signed and initialed, of this Form

1449 with the next communication. If the Examiner is missing page one of this Form 1449 or the associated references, Applicants can provide copies upon the Examiner's request.

The following remarks are organized in accordance with the statute under which the claims are rejected.

Rejection of Claims 1, 2, 4, 5, 7-9, 11-17, 19, 20, and 39-59 Under 35 U.S.C. §112, First Paragraph:

The Examiner has rejected Claims 1, 2, 4, 5, 7-9, 11-17, 19, 20, and 39-59 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the methods of cloning a transgenic animal, comprising introducing a G_1 nucleus from an activated donor cell into an activated oocyte of the same species in telophase II of meiosis or an enucleated oocyte of telophase to meiotic structure to form a mammalian reconstructed embryo, fusing the reconstructed embryo, and transferring the embryo to a recipient mammal of the same species to produce a mammal as claimed and a method of producing a mammalian nuclear transfer embryo, comprising a G_1 nucleus from a somatic activated donor cell with a activated enucleated oocyte in telophase II and of the same species as the donor cell, and fusing the nucleus and oocyte to thereby form a nuclear transfer embryo, does not reasonably provide enablement for the methods as claimed. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner further stated that fusion is required for the integration of the oocyte and donor nucleus or donor cell membranes, and that without fusion the membranes of the donor nucleus or donor cell would remain intact and the donor nucleus would not be available for reprogramming by the cytoplasm of the enucleated oocyte recipient.

Applicants amend Claims 1, 2, 8, 9, 11, 17, 39, 40, 44, 45, 47, 48, 49, 51 so that they include fusion of the donor cell and the enucleated oocyte. Accordingly, Applicants have overcome this portion of the rejection.

Applicants also add Claims 84-93, which state that the nucleus of the donor cell is injected into the enucleated oocyte, rather than fusing the two cells. The specification indicates that the combination of an activated, enucleated oocyte with the nucleus of the activated donor

cell can occur in a variety of ways. These include, for example, fusing the donor cell and the enucleated oocyte, or injecting the contents of the donor cell including its nucleus into the enucleated oocyte. The Examiner states that fusion is required for the integration of the oocyte and donor nucleus or donor cell membranes. Although this may be so for some embodiments of the invention, fusion of the cells does not have to occur in all embodiments. Rather, as an alternative, injection of the nucleus of the donor cell into an enucleated oocyte allows for the cytoplasm of the enucleated oocyte recipient to be reprogrammed, and for the invention, as claimed, to be carried out. Hence, in this embodiment, the membrane of the donor cell would not interfere with embryo development. Accordingly, Claims 84-93 meet the requirements of 35 U.S.C. §112, first paragraph.

The Examiner also stated that successful transfer requires that the donor nucleus be diploid, and the only nuclei that are diploid are those in G_0 or G_1 phases. Applicants amend Claims 2, 9, 17, and 40 and add new claims 60, 64, 68, 72, 76, and 80 so that they include the G_1 phase.

The Examiner further rejected Claims 21-26 and 28-30 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the methods where the donor cells are transformed *in vitro* prior to the nuclear transfer procedure into an enucleated oocyte in telophase II. Furthermore, the Examiner states that transgenic animals have cellular mechanisms which prevent expression of the transgene, and that the elements of the particular construct used to make transgenic animals were held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene, e.g. specific promoters, presence or absence of introns, etc.

Applicants have cancelled Claims 21-26 and 28-30. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection of Claims 31, 32, 34, 35, 36 and 38 Under 35 U.S.C. §102(b)

The Examiner rejected Claims 31, 32, 34, 35, 36 and 38 under 35 U.S.C. §102(b) as being clearly anticipated by Bordignon, *et al.*, *Molec. Reprod. Devel.* 49:29-36 (1998) (hereinafter "Bordignon, *et al.*"). The Examiner stated that Bordignon, *et al.* teach enucleation of telophase nuclei which have mitotic spindle apparatus, by incubating the nuclei in cytochalasin

B. The Examiner further stated that both the meiotic spindle apparatus and chromosomes were destabilized as evidence by fragmented chromatin in the first polar body, and that the surrounding media was altered, as evidenced by the inclusion of Hoechst 33342. Additionally, the Examiner rejected Claims 35, 36, and 38 for these reasons and further because, in Bordignon, *et al.*, the oocytes were activated by exposure to ethanol. Therefore, the Examiner states that Bordignon, *et al.* clearly anticipate the claimed invention.

Applicants cancelled Claims 31, 32, 34-36 and 38 and, thereby obviate this portion of the rejection. Applicants respectfully request withdrawal of this rejection.

Rejection of Claims 31, 33, 35, and 37 Under 35 U.S.C. §103(a)

The Examiner has rejected Claims 31, 33, 35 and 37 under 35 U.S.C. §103(a) as being unpatentable over Bordignon, *et al.* in view of Kono, *Rev. of Reprod.* 2:74-80 (1997) (hereinafter "Kono") and Molecular Biology of the Cell, Second Edition, Alberts, *et al.*, Garland Publishing, Inc., pp 652-653 (hereinafter "Molecular Biology"). The Examiner states that Bordignon, *et al.* teach the enucleation of telophase nuclei which have a mitotic spindle apparatus by incubating the nuclei and cytochalasin B. The Examiner further states that meiotic spindle apparatus and chromosomes were destabilized as evidence by fragmented chromatin in the first polar body. The Examiner further states that the oocytes were activated by exposure to ethanol, however Bordignon, et al. does not teach destabilization of the mitotic spindle apparatus using demecolcine, nocodazole, colchicine or paclitaxel. The Examiner further indicates that Kono teaches that nocodazole inhibits tubulin polymerization and thus this compound would destabilized the meiotic spindle apparatus. Also, the Examiner indicates that Molecular Biology teaches that colchicine and paclitaxel also known as taxual are destabilizers of tubulin and mitotic spindle apparatus.

Applicants have cancelled Claims 31, 33, 35 and 37, and, as such, withdrawal of the instant rejection respectfully is requested.

SUMMARY AND CONCLUSIONS

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Twice Amended) A method of cloning a mammal, comprising the steps of:
   a. [combining] fusing [a nucleus from] a somatic activated donor cell [with] and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a nuclear transfer embryo;
   b. impregnating a mammal of the same species as the nuclear transfer embryo with the fused nuclear transfer embryo under conditions suitable for gestation of the cloned mammal; and
   c. gestating the embryo in step b., thereby causing the embryo to develop into the cloned mammal.

2. (Amended) The method of Claim 1, wherein the activated donor cell is in [a] the G_1 stage of a mitotic cell cycle [selected from the group consisting of: G_1 phase, S phase, and G_2/M phase].

8. (Twice Amended) A method of producing a transgenic mammal, comprising the steps of:
   a. [combining] fusing [a genetically engineered nucleus from] a somatic activated donor cell having a genetically engineered nucleus [with] and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a transgenic nuclear transfer embryo;
   b. impregnating a mammal of the same species as the nuclear transfer embryo with the fused, [transgenic] nuclear transfer embryo under conditions suitable for gestation of the transgenic mammal; and
   c. gestating the embryo in step b., thereby causing the embryo to develop into the transgenic mammal.

9. (Amended) The method of Claim 8, wherein the activated donor cell is in [a] the G_1 stage of a mitotic cell cycle [selected from the group consisting of: G_1 phase, S phase, and G_2/M phase].

11. (Twice Amended) A method of producing a mammalian nuclear transfer embryo, comprising [combining a nucleus from] fusing a somatic activated donor cell [with] and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a nuclear transfer embryo.

17. (Twice Amended) The method of Claim 16, wherein the somatic activated donor cell is in [a] the G_1 stage of a mitotic cell cycle [selected from the group consisting of: G_1 phase, S phase, and G_2/M phase].

39. (Amended) A method of cloning a mammalian fetus, comprising the steps of:

a. [combining] fusing [a nucleus from] a somatic activated donor cell [with] and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a nuclear transfer embryo;

b. impregnating a mammal of the same species as the nuclear transfer embryo with the fused nuclear transfer embryo under conditions suitable for gestation of the cloned mammalian fetus; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the cloned mammalian fetus.

40. (Amended) The method of Claim 39, wherein the activated donor cell is in [a] the G_1 stage of a mitotic cell cycle [selected from the group consisting of: G_1 phase, S phase, and G_2/M phase].

44. (Amended) A method of cloning a non-human mammal, comprising the steps of:

a. [combining] fusing [a nucleus from] a somatic activated donor cell [with] and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a nuclear transfer embryo;

b. impregnating a non-human mammal of the same species as the nuclear transfer embryo with the fused nuclear transfer embryo under conditions suitable for gestation of the cloned non-human [cloned] mammal; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the cloned non-human [cloned] mammal.

45. (Amended) A method of producing a transgenic non-human mammal, comprising the steps of:

a. [combining] fusing [a genetically engineered nucleus from] a somatic activated donor cell [with] having a genetically engineered nucleus and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a transgenic nuclear transfer embryo;

b. impregnating a non-human mammal of the same species as the nuclear transfer embryo with the transgenic nuclear transfer embryo under conditions suitable for gestation of the transgenic non-human mammal; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the transgenic non-human mammal.

47. (Amended) A method of cloning a non-human mammalian fetus, comprising the steps of:

a. [combining] fusing [a nucleus from] a somatic activated donor cell [with] and an activated, enucleated oocyte in telophase II and of the same species as the donor cell, to thereby form a nuclear transfer embryo;

b. impregnating a non-human mammal of the same species as the nuclear transfer embryo with the fused nuclear transfer embryo under conditions suitable for gestation of the cloned non-human mammalian fetus; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the [cloned] non-human mammalian fetus.

48. (Amended) A method of cloning a mammal, comprising the steps of:

a. [combining] fusing [a nucleus from] a somatic activated donor cell [with] and an activated, enucleated oocyte derived from an oocyte having a first polar body and an extruding second polar body, and of the same species as the donor cell, to thereby form a nuclear transfer embryo;

b. impregnating a mammal of the same species as the nuclear transfer embryo with the fused nuclear transfer embryo under conditions suitable for gestation of the cloned mammal; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the cloned mammal.

49. (Amended) A method of producing a transgenic mammal, comprising the steps of:

a. [combining] fusing [a genetically engineered nucleus from] a somatic activated donor cell [with] having a genetically engineered nucleus and an activated, enucleated oocyte derived from an oocyte having a first polar body and an extruding second polar body, and of the same species as the donor cell, to thereby form a transgenic nuclear transfer embryo;

b. impregnating a mammal of the same species as the nuclear transfer embryo with the fused transgenic nuclear transfer embryo under conditions suitable for gestation of the transgenic mammal; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the transgenic mammal.

51. (Amended) A method of [cloning] producing a mammalian fetus, comprising the steps of:

a. [combining] fusing [a nucleus from] a somatic activated donor cell [with] and an activated, enucleated oocyte derived from an oocyte having a first polar body and an extruding second polar body, and of the same species as the donor cell, to thereby form a nuclear transfer embryo;

b. impregnating a mammal of the same species as the nuclear transfer embryo with the fused nuclear transfer embryo under conditions suitable for gestation of the [cloned]

mammalian fetus; and

c. gestating the embryo in step b., thereby causing the embryo to develop into the [cloned] mammalian fetus.